Amlodipine poisoning management

KC Mothata-Motswaledi, E Osuch

Department of Pharmacology and Therapeutics, School of Medicine, Sefako Makgatho Health Science University, South Africa

Corresponding author, email: Elzbieta.Osuch@smu.ac.za

Amlodipine is a commonly used calcium-channel blocker (CCB) used in the treatment of hypertension. Severe CCB toxicity is highly lethal, as a result of cardiovascular collapse. Amlodipine overdose can lead to prolonged hypotension and potent vasodilatation which can result in fatality. Early identification of CCB overdose can save lives and reduce the risk of complications. The management of CCB intoxication will be reviewed.

Keywords: amlodipine overdose, calcium-channel blockers toxicity, high-dose insulin euglycaemic therapy (HIET), lipid emulsion therapy, hypotension

Introduction

The CCBs have different effects on the cardiac rate, contractility and heart conduction and therefore are divided into two major categories based upon their predominant physiological effects: dihydropyridines (amlodipine, felodipine, nifedipine, lercanidipine) and non-dihydropyridines (verapamil, diltiazem). The dihydropyridines preferentially affect vascular smooth muscle, thereby decreasing peripheral vascular resistance, reducing afterload and lowering blood pressure. They are therefore used in the management of hypertension and angina pectoris. The non-dihydropyridines have more significant myocardial effects thereby decreasing conduction and heart rate. They are therefore preferentially used in supraventricular arrhythmias and angina including Prinzmetal’s angina. However, in overdose, receptor selectivity may be lost, so even dihydropyridines may cause cardiotoxicity in addition to vasodilation in large overdoses.

CCBs act by reducing calcium ion entry via the voltage gated L type calcium channels thus reducing release of calcium from the sarcoplasmic reticulum and thereby reducing contractility of myocardial and vascular smooth muscle. Calcium channels are functionally important not only in cardiac myocytes and vascular smooth muscle cells but also in islet beta cells of the pancreas, the central nervous system and skeletal muscle. Therefore blockade of calcium channels in the pancreatic beta cells can cause reduced insulin release.

Ingestion of excessive CCBs, either accidental or in deliberate self-harm, is one of the most potentially lethal drug overdoses. The exact toxic dose has not been fully established, however it is recommended that adult patients be monitored for toxicity if more than 10 mg amlodipine was ingested (> 0.3 mg/kg in children). Verapamil and diltiazem are the most lethal CCBs in overdose and the patient should be monitored if more than 120 mg verapamil immediate-release or more than 480 mg verapamil sustained-release (> 2.5 mg/kg in children) was ingested.

Pharmacokinetics

All subtypes of CCBs are very well absorbed orally, undergo extensive hepatic first-pass metabolism (metabolised by cytochrome P450 system). CCBs are lipophilic, bind highly to plasma proteins and have a large volume of distribution (> 2 liters/kg) so elimination by haemodialysis or haemofiltration is ineffective. They are excreted mostly in the urine. At higher doses, clearance slows, because hepatic clearance changes from first-order to zero-order kinetics. Amlodipine has an elimination half-life of approximately 30 to 50 hours while verapamil's half-life is shorter up to eight hours (up to 12 hours in repeated doses).

Diagnosis of the overdose

The diagnosis of CCB poisoning is made clinically on the basis of the history and clinical findings. Typically there is a history of overdose combined with hypotension. Patients may maintain a clear mental status despite hypotension and bradycardia. Patients with significant CCB ingestion can deteriorate rapidly. Whenever possible, the time of ingestion as well as the type, amount, and preparation (immediate- or sustained-release) of drug ingested should be determined. It is important to clarify whether the ingestion was accidental or intentional and to assess the patient for suicidality.

The hallmark of CCB overdose is circulatory shock due to bradycardia, poor cardiac contractility and profound peripheral vasodilatation, which leads to tissue hypoperfusion and target organ damage. CCBs of all subclasses reduce pancreatic insulin secretion and induce end-organ insulin resistance causing hyperglycaemia. Metabolic side-effects include hyperglycaemia, hypoinsulinaemia and impairment of the cardiac myocyte adaptive response. Additionally, CCBs interfere with calcium-stimulated mitochondrial action and glucose catabolism which can result in lactate production and ATP hydrolysis contributing to acidosis. Significant bradycardia, hypotension, second- and third-degree heart block can occur especially with verapamil
intoxication while amlodipine causes hypotension and reflex sinus tachycardia. Complications may include myocardial ischaemia, stroke and non-occlusive mesenteric ischaemia. Neurological presentations with seizures and coma are rare, however, they can occur as a late feature of toxicity due to cardiovascular collapse. Clinical toxicity of CCB usually begins within 30–60 minutes of overdose ingestion, however, with slow-release preparations the onset of significant toxicity may be delayed to 12–16 hours with peak effects after 24 hours.

Investigations and laboratory evaluation

Monitoring of blood pressure, heart rate, oxygen saturation, and arterial blood gas analysis should be done and metabolic and lactic acidosis should be corrected promptly. ECG and echocardiography should be performed to exclude PR interval prolongation, brady-dysrhythmia and impaired cardiac contractility. Serum electrolytes, blood urea nitrogen (BUN), creatinine, calcium, and glucose concentrations should be assessed. A chest radiograph should be obtained if there are any signs of pulmonary oedema, hypoxia, or respiratory distress. Laboratory assays for CCBs are not routinely available and do not aid to the management.

Overdose management

Asymptomatic patients with normal vital signs require monitoring for at least 12 hours with standard-release preparations and for at least 24–36 hours if sustained/extended-release or once-a-day preparation was ingested. Activated charcoal (AC) as a single dose of 1 g/kg for children up to the adult dose of 50 g should be administered to patients within one hour of ingestion for standard-release preparations and within four hours of ingestion for SR preparations. AC should be administered even if the patient is asymptomatic but must be withheld in patients who cannot protect their airway and in patients with a depressed mental status. Orogastric lavage may be necessary in patients who present within one to two hours of a potentially dangerous ingestion and lactic acidosis should be corrected. A bolus of bicarbonate may be given and a maintenance infusion should be started.

The initial management consists of airway stabilisation and intravenous administration of isotonic crystalloid for hypotension. Early intubation and ventilation when life-threatening hypoxia occurs. High-dose insulin euglycaemic therapy (HIET) should be initiated if there is no haemodynamic improvement with adrenergic agents. It has shown to restore haemodynamic stability where high doses of multiple vasopressors have failed. Relative hypoglycaemia and hypokalaemia must be corrected prior to initiating high-dose insulin therapy. HIET is given as a loading dose of 1 IU/kg short-acting insulin intravenously, simultaneously starting an infusion of 1–10 IU/kg/hour, to achieve haemodynamic stability. A loading dose of insulin should be given together with a loading dose of 1 ml/kg of 50% dextrose water, followed by an infusion of 10% dextrose to maintain normoglycaemia. Glucose testing should be done 30 minutes after HIET and then hourly thereafter.

Expected complications of HIET are hypoglycaemia and hypokalaemia. Hyperglycaemia due to CCB overdose is often refractory to high-dose insulin. Therefore, not all patients require supplemental dextrose and only patients with a serum glucose concentration below 8 mmol/L should receive treatment with 50 ml of 50% dextrose. For patients with a serum potassium concentration below 3 mEq/L (3 mmol/L), 20 mEq of potassium IV should be administered.

Administration of calcium will promote calcium influx via unblocked L type calcium channels, however, responses are variable and suboptimal with severe toxicity. Calcium may improve hypotension, and conduction disturbances but is less effective in the management of bradycardia. Two-hourly monitoring of serum or ionised calcium concentration and serial electrocardiograms (ECGs) is recommended to avoid clinically significant hypercalcaemia.

Lipid emulsion therapy could be considered in refractory cases. Intravenous lipid emulsion is an oil-in-water emulsion that creates a lipid phase within the plasma and thus pulls a lipid-soluble drug into the lipid phase in blood. Lipid emulsion infusion can sequester intensely lipophilic drugs like verapamil and diltiazem and reduce their volume of distribution. Infusion of lipid emulsion also provides a sustained fatty acid energy source to the myocardium. Adverse effects of lipid emulsion therapy include acute pancreatitis, ARDS, interference with vasopressors and fat overload syndrome inducing hepatosplenomegaly, seizures, fat embolism, and coagulopathy.

Other interventions in refractory cases as an adjuvant to vasopressors and HIET may include transvenous cardiac pacing, an intraaortic balloon pump and extracorporeal membrane oxygenation and cardiopulmonary bypass.

Differential diagnosis

Initial presentation with bradycardia and hypotension could be signs of toxicity of various pharmacological agents including beta blockers, tricyclic antidepressants, digoxin, clonidine, sedative-hypnotics, opioids and organophosphate poisoning. The presence of hyperglycaemia in a nondiabetic patient may help to distinguish CCB from beta blocker poisoning.
Amlodipine poisoning management

Table 1: Specific therapies in CCB overdose

<table>
<thead>
<tr>
<th>CCB overdose</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stabilise airway, breathing and circulation</td>
<td><strong>Stabilisation of the airway as necessary (avoid induction agents that exacerbate hypotension). Fluid resuscitation 500 mL to 1 000 mL isotonic saline.</strong> (up to 20 mL/kg crystalloid).</td>
</tr>
<tr>
<td>Gastrointestinal decontamination</td>
<td>Activated charcoal (1 g/kg up to 50 g maximum) in patients who are haemodynamically stable with normal mental status. Whole bowel preparation (2 L/hour by mouth until clear rectal effluent) for potentially life-threatening ingestion of extended-release preparation.</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Atropine IV 0.5–1.0 mg boluses, may repeat up to 3 total doses (0.02 mg/kg IV in paediatric patients).</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Vasopressors IV: Adrenaline infusion 0.05–1 µg/kg/min. Note: Inotropic actions predominate at lower doses with vasoconstrictive actions at higher doses. Noradrenaline at 2 mcg/mg/minute IV, titrated until systolic BP is 100 mmHg.</td>
</tr>
<tr>
<td>Hypotension and/or bradycardia</td>
<td>Intravenous calcium salts: Calcium gluconate Bolus of 60 mL of 10% solution IV (0.6–1.0 mL/kg in children) OR calcium chloride 10 to 20 mL of 10% solution (0.2 mL/kg in children) via a central line. Repeat boluses can be given up to 3 times. Monitor serum level and ECG to exclude hypercalcaemia. High dose insulin therapy (HIET) and dextrose: Loading dose of 50% dextrose 1 mL/kg IV. Bolus of 1 unit/kg IV of regular insulin and be maintained at an infusion of 0.5 units/kg per hour. Maintained at 10% dextrose infusion to maintain normoglycaemia based on hourly glucose measurements. Glucagon IV administered at a dose of 1 to 5 mg IV and may be repeated twice. Nausea, vomiting, hyperglycaemia, hypokalaemia, and ileus can occur with bolus doses above 50 micrograms/kg. Lipid emulsion therapy (20% solution) administered at a bolus of 1.5 mL/kg over 2 minutes. The same dose may be repeated every three to five minutes if there is no response, for a total of three bolus doses. Infusion 1.5 mL/kg over 60 minutes.</td>
</tr>
<tr>
<td>Severe metabolic acidosis</td>
<td>Sodium bicarbonate Adults: 8.4% sodium bicarbonate solution administered at a dose of 1 mEq/kg up to a maximum dose of 50 mEq, as an IV slow push and repeat doses should be guided by arterial blood gases. Infusion 0.5 mEq/kg over 60 minutes.</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>Potassium chloride infusion at rate 10 mmol/h. *meq – milliequivalent, ECG – electrocardiogram, BP – blood pressure</td>
</tr>
</tbody>
</table>

**Conclusion**

Severe CCB poisoning is life-threatening, and management is often challenging and requires immediate treatment. Clinicians should familiarise themselves with its management. Good outcomes can be achieved through aggressive treatment and provision of circulatory support. Psychiatric assessment in case of parasuicide is of paramount importance.

**References**


